The Roles of Mitochondrial Free Radicals and Uncoupling Proteins in the Short- and Long-Term Responses to Nutrients in Pancreatic β-Cells

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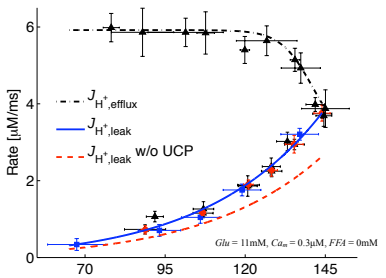
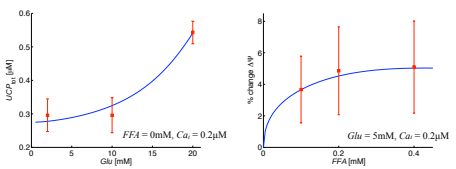
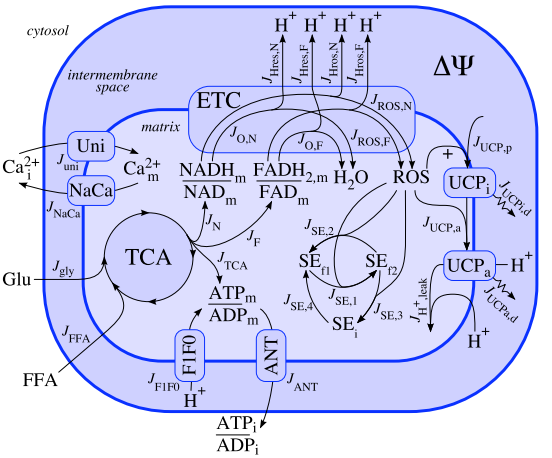
Abstract: Pancreatic β-cells sense the ambient blood-glucose concentration and secrete insulin to signal other tissues to take up glucose. Mitochondria play a key role in this response as they metabolize nutrients to produce ATP and reactive oxygen species (ROS), both of which are involved in insulin secretion signaling. Based on data available in the literature and previously derived models, we present a model of β-cell mitochondrial respiration, ATP synthesis, and ROS production and control in response to glucose and fatty acid stimulation. The model is consistent with a number of experimental observations reported in the literature. Most notably, it captures the nonlinear rise in the proton leak rate at high membrane potential and the increase in this leak due to uncoupling protein (UCP) activation by ROS. The functional forms used to model ROS production and UCP regulation yield insight into these mechanisms, as many details have not yet been unraveled in the experimental literature. We examine the short- and long-term effects of UCP activation inhibition and changes in the mitochondrial density on mitochondrial responses to glucose. Results from the model support the hypothesis that long-term elevated fatty acid exposure may inhibit glucose-stimulated insulin secretion (GSIS), and suggest that increasing mitochondrial density while decreasing UCP activity may be an effective way to increase GSIS while decreasing oxidative stress. The model may also be useful in a clinical setting, such as to predict the insulin secretion rate and quantify β-cell function from the glucose and fatty acid profiles of an individual.

Proton leak rate: A nonlinear relationship exists between the proton-leak rate and the membrane potential. UCP account for approximately 30% of this leak in beta-cells.



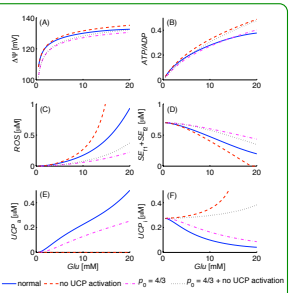
Additional parameterization:

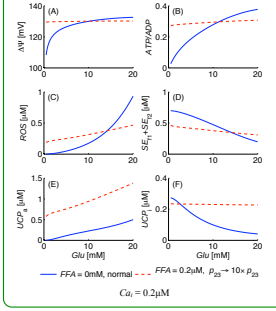




Nomenclature: Glu: plasma glucose, FFA: plasma free fatty acids, TCA: tricarboxylic acid cycle, Ca_i: intracellular calcium, Ca_m: mitochondrial calcium, Uni: Ca^{2+} uniporter, NaCa: Na^+/Ca^{2+} exchanger, ETC: electron transport chain, H^+: protons, ROS: reactive oxygen species, **ΔΨ**: mitochondrial inner membrane potential, UCP_i: inactive uncoupling protein, UCP_a: active uncoupling protein, SE_{ox}: oxidized scavenging enzyme, SE_{rd}: reduced scavenging enzyme, SE: inhibited scavenging enzyme, ANT: adenine nucleotide translocator, F1F0: F_1F_0-ATP synthase.

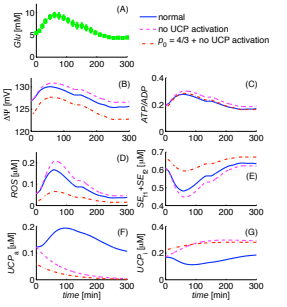
Long-term responses to glucose: Long-term UCP activation inhibition causes sustained increases in ROS levels, and thus oxidative stress, but distributing the metabolic load by increasing the mitochondrial density (p_0) improves the ATP/ADP response while keeping ROS levels low.



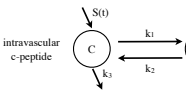


Effects of long-term elevated FFA exposure: FFA treated β-cells have increased basal insulin secretion, but decreased glucose-stimulated insulin secretion. They also have more UCP. Model simulations suggest FFA could cause this crossover effect by increasing the ROS-dependent UCP-production signal (p_{23}).

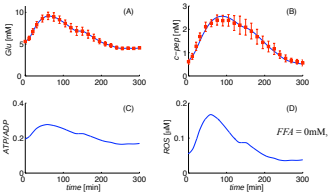
Short-term responses to glucose: ROS signaling and the ATP/ADP response are improved with acute inhibition of UCP activity.



Insulin and c-peptide secretion model: Our model can be incorporated into a c-peptide model to predict the insulin secretion rate and provide a quantitative description of β-cell function for a single individual.



$$\frac{dC(t)}{dt} = -(k_1 + k_3)C(t) + k_2 Y(t) + S(t)$$
$$\frac{dY(t)}{dt} = k_1 C(t) - k_2 Y(t)$$
$$S(t) = k_a \frac{ATP}{ADP} + k_r ROS - k_b$$



Conclusions: Our model is consistent with a number of experimental observations reported in the literature: the most notable of which is the nonlinear proton-leak rate as a function of mitochondrial membrane potential. We can use the model to propose hypotheses related to insulin secretion and the effects of ROS, UCP, and mitochondrial density on pancreatic β-cell function. Model results suggest that increasing mitochondrial density while decreasing UCP activity may be an effective way to increase GSIS while decreasing oxidative stress. Our model may also be useful in a clinical setting to predict the c-peptide and insulin secretion rates and quantify β-cell function in an individual based on time-course profiles of blood-glucose and free fatty acid concentrations.

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